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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Chih-Pin LIU, et al.	)	
	)	
Serial No. 10/074,257	)	Examiner: Francois P. Vandervegt
	)	
Filed: February 14, 2002	)	Group Art Unit: 1644
	)	
For: ANTIGEN SPECIFIC RECOMBINANT MHC CLASS II MOLECULES AND METHOD OF USE	)	Confirmation No. 5061

DECLARATION UNDER 37 C.F.R. §1.132

Dear Sir:

I, Chih-Pin Liu, do solemnly declare that:

1. I am the same Chih-Pin Liu listed as an inventor on the above-referenced patent application.

2. I received a B.S. in biochemistry from National Taiwan University, ROC in 1983, an M.S. in microbiology from the University of Minnesota in 1988, and a Ph.D. in immunology from the University of Wisconsin in 1991. I received post-doctoral training in the Division of Immunology at Beth Israel Hospital/Harvard Medical School in Boston, Massachusetts and at the Howard Hughes Medical Institute, National Jewish Center for Immunology/Respiratory Medicine in Denver, Colorado. In 1998, I became an Assistant Professor in the Division of Immunology at the Beckman Research Institute of the City

of Hope. I have since been promoted to the rank of Associate Professor in the Division of Immunology at the Beckman Research Institute and hold a joint appointment at the Department of Diabetes, Endocrinology and Metabolism at the Beckman Research Institute. A copy of my curriculum vitae is attached herewith as Exhibit 1.

3. I have reviewed and am familiar with U.S. Patent Application Serial No. 10/074,257, filed February 14, 2002, Entitled "Antigen Specific Recombinant MHC Class II Molecules and Methods of Use", including the claims currently pending in the application as amended in the response filed concurrently herewith. I also have reviewed and am familiar with the Office Action of November 3, 2004 and the references cited therein.

4. The claims currently pending in the application are directed to recombinant nucleic acids that contain DNA which encodes an autoantigen peptide that binds to a Class II molecule and which encodes the extracellular portion of the β chain of that Class II molecule. These nucleic acids are useful in producing reagents which can identify and isolate T cells involved in autoimmune disease such as Type 1 diabetes.

5. In the outstanding Office Action, the examiner has asserted that it would be obvious to combine the Z'hu et al. reference, which discusses class II MHC with antigenic

peptides, and the Chao et al. reference, which provides GAD peptide epitopes, and that these references provide motivation for the combination, which would have a reasonable expectation of success. The examiner has rejected claims in this application based on grounds of obviousness over these two references.

6. I applied to the National Institutes of Health for a pilot grant to generate class II MHC tetramers that would allow us to identify and isolate T cells involved in autoimmune disease (specifically Type 1 diabetes). The reviewers of this grant application expressed the opinion that the proposed approaches were new and could be highly rewarding if they worked, but also expressed doubt that they would work, stating that this work was risky and not likely to succeed. In summary, the grant reviewers believed that we would not succeed in generating class II MHC tetramers in general and that it was more questionable that we could produce such tetramers for autoimmune disease-associated class II MHC genes containing autoantigenic peptides. In my opinion, the art at the time this application was filed taught that discovering peptides that bind to class II MHC molecules was unpredictable and risky. See Hackett and Sharma, *Nat. Immunol.* 3(10): 887-889, 2002. Therefore, it is my opinion that the art provided no expectation of

success for the invention claimed in this application, much less a reasonable expectation of success.

7. In my opinion, ours is the first research group to generate such autoimmune disease-associated class II MHC tetramer reagents and to use them to isolate large numbers of autoreactive T cells. Since the time of filing of this patent application, we have generated several tetramer reagents containing autoantigenic peptides and have been able to identify and isolate T cells specific for the autoantigens.

8. It is my opinion that it would not have been obvious to achieve the invention claimed in the accompanying patent application because, among other reasons, the skilled person would not have had a reasonable expectation of success when combining any particular peptide with the class II MHC molecules described in our application.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Chih-Pin Liu

1-28-2005

Date

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BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format on for each person. (See attached sample). **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Chih-Pin Liu	Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
National Taiwan University, ROC	B.S.	1983	Biochemistry
University of Minnesota, Minneapolis, MN	M.S.	1988	Microbiology
University of Wisconsin, Madison, WI	Ph.D.	1991	Immunology

A. Positions & Honors:

Positions:

2003 - present Associate Professor, Department of Diabetes, Endocrinology, and Metabolism, Beckman Research Institute, City of Hope, Duarte, CA

2003 - present Associate Professor, Division of Immunology, Beckman Research Institute, City of Hope, Duarte, CA

1998 - 2003 Assistant Professor, Division of Immunology, Beckman Research Institute, City of Hope, Duarte, CA.

1994 - 1997 Research Associate, Howard Hughes Medical Institute, National Jewish Center for Immunology/Respiratory Medicine, Denver, CO.

1991 - 1993 Research Fellow, Department of Medicine, Division of Immunology, Beth Israel Hospital/Harvard Medical School, Boston, MA.

1988 - 1991 Research Assistant, Department of Zoology, University of Wisconsin, Madison, WI.

1985 - 1988 Research Assistant, Department of Microbiology, University of Minnesota, Minneapolis, MN.

1983 - 1984 Research Assistant, Department of Agricultural Chemistry, National Taiwan University, Taiwan, R.O.C.

Honors:

1992-1994 Cancer Research Institute Postdoctoral Fellowship

1991 Sigma Xi Graduate Student Research Award finalist, Wisconsin Chapter.

1991 Jefferson Davis Fund Predoctoral Fellowship.

1989 Jefferson Davis Fund Travel Award.

B. Selected Peer Reviewed Publications:

1. Zhong, L., Wu, C.-H., Lee, W.-H., and Liu, C.-P. 2004. ZAP-70, but not Syk, tyrosine kinase can mediate apoptosis of T cells through the Fas/FasL, caspase-8, and caspase-3 pathways. J. Immunol. 172:1472-1482.
2. You, S., Chen, C., Lee, W.-H., Brusko, T., Atkinson, M., and Liu, C.-P. 2004. Presence of diabetes-inhibiting glutamic acid decarboxylase-specific IL-10-dependent regulatory T cells in naive NOD mice. J. Immunol. 173:6777-6785.
3. Krymskaya, L., Lee, W.-H., Zhong, L., and Liu, C.-P. 2005. Polarized development of memory cell-like IFN-γ-producing cells in the absence of TCR ζ chain. J. Immunol. 174: In Press.

4. Chen, C.L., Lee, W.-H., Pen, Y., Snow, P., Liu, C.-P. 2003. Induction of autoantigen-specific Th2 and Tr1 regulatory T cells and modulation of autoimmune diabetes. J. Immunol. 171:733-744.
5. You, S., Chen, C., Lee, W.-H, Wu, C.-H., Judkowski, V., Pinilla, C., Wilson, D.B., and Liu, C.-P. 2003. Detection and characterization of T cells specific for BDC2.5 T cell-stimulating peptides. J. Immunol. 170:4011-4020.
6. Lee, W.-H., Ramos, T., Krymskaya, L., and Liu, C.-P. 2003. Development of T cells expressing an altered TCR complex. Eur. J. Immunol. 33:2696-2705.
7. Liu, C.-P., Jiang, K., Wu, C.-H., W.-H. Lee, and Lin, W.-J. 2000. Detection of glutamic acid decarboxylase (GAD) activated T cells with I-A^{g7} tetramers. Proc. Nat'l Acad. Sci. USA, 97:14596-14601.
8. Liu C.-P., Crawford, F., Marrack, P., and Kappler J. 1998. T cell positive selection by a high density, low affinity ligand. Proc. Nat'l. Acad Sci. USA, 95:4522-4526.
9. Liu C.-P., Parker, D., Kappler J., and Marrack, P. 1997. Selection of antigen-specific T cells by a single IE^k/peptide combination. J. Exp. Med. 186: 1441-1450.
10. She J., Simpson, S. J., Gupta, A., Hollander, G., Levelt, C., Liu, C.-P., Allen, D., van Houten, N., Wang, B., Terhorst, C. 1997. CD16-expressing $CD8\alpha\alpha^+$ T lymphocytes in the intestinal epithelium: Possible precursors of $Fc\gamma R^-CD8\alpha\alpha^+$ T cells. J. Immunol. 158: 4678-4687.
11. Liu C.-P., Lin, W.-J., Huang, M., Kappler J., and Marrack, P. 1997. Development and function of T cells in TCR/CD3 ζ-gene knockout mice expressing FcεRIγ. Proc. Nat. Acad. Sci. 94: 616-621.
12. Marrack P., Ignatowicz, L., Parker, D., Liu, C.-P., and Kappler, J. 1996. The structure and specificity of T cells selected by a single MHC/peptide combination. In "HLA and Disease – The Molecular Basis". Alfred Benzen Symposium 40. Published by Munks Goard Copenhagen
13. Liu C.-P., Kappler J., and Marrack, P. 1996. Thymocytes can become mature T cells without passing through the $CD4^+CD8^+$ double positive stage. J. Exp. Med. 184: 1619-1630.
14. Wang B., Levelt C., Salio M., Zheng D., Sancho J., Liu C.-P., She J., Huang M., Higgins K., Sunshine M.-J., Eichmann K., Lacy E., Lonberg N., and Terhorst C. 1995. Over-expression of CD3ε transgenes blocks T lymphocyte development. Internatl. Immunol. 7: 435-448.
15. Liu C.-P., Ueda R., She J., Sancho J., Wang B., Weddell G., Loring J., Kurahara C. , Dudley E. C., Hayday A., Terhorst C., and Huang M. 1993. Abnormal T cell development in CD3 $\zeta^{-/-}$ mutant mice and identification of a novel T cell population in the intestine. The EMBO J. 12: 4863-4875.
16. Liu C.-P., Globerson A. and Auerbach R. 1993. A cloned lymphoid Thy1+ tumor line derived from murine yolk sac cells maintained in long-term cell culture in the absence of a thymic microenvironment expresses an unusual cell surface phenotype. Thymus. 21:221-233.
17. Liu C.-P., and Auerbach R. 1991b. In vitro development of murine T cells from pre-thymic and pre-liver embryonic yolk sac stem cells. Development. 113: 1315-1323.
18. Liu C.-P., and Auerbach R. 1991a. Ontogeny of murine T cells: Thymus regulated development of T cell receptor-bearing cells derived from embryonic yolk sac. Eur. J. Immunol. 21:1849-1855.
19. Wu S., Lu D., Madden M., Liu C.-P., Miyokawa N., Bach F.H., and Saunders T.L. 1990. Full-length DQ β cDNA sequences of HLA-DR2/DQw1 subtypes: Genetic interactions between two DQ β loci generate human class II HLA diversity. Human Immunol. 27:305-322.
20. Liu C.-P., Wu S., and Bach F.H. Molecular studies of a rare HLA haplotype: Implications for mechanisms of generating class II gene polymorphisms. In Dupont B. (ed.): Immunobiology of HLA, vol. II: Immunogenetics and Histocompatibility. Springer-Berlag, NY, 1989; pp. 194-197.
21. Liu C.-P., Bach F.H., and Wu S. 1988. Molecular studies of a rare DR2/LD-5a/DQw3 HLA class II haplotype: Multiple genetic mechanisms in the generation of polymorphic HLA class II genes. J. Immunol.140:3631-3639.

C. Research Support Completed/Ongoing During the Last Three Years

Ongoing Research Support:

1. R01 AI48847 2/1/01 - 1/31/06
   National Institute of Health
   "Regulatory Mechanisms in Type 1 Diabetes"
   This is a continuation of R21 AI44429. The major goals of the proposed studies are to continue determining the mechanisms by which autoantigen-specific T cells, isolated using tetramers, may regulate the development of autoimmune diabetes.
   Role: P.I.

2. P30 CA033572 4/1/04 - 3/31/06
   National Institute of Health
   Cancer Center Developmental Funding Support
   "Identification and characterization of tumor antigen-specific $CD4^+$ T cells"
   The major goal of this award is to perform preliminary studies to isolate and characterize tumor antigen-specific $CD4^+$ T cells.
   Role: P.I.

Completed Research Support:

1. R01 AI44143 3/1/99 - 2/28/04
   National Institute of Health
   "Influence of TCR/CD3 Complex on T Cell Development"
   The major goals of these studies are to determine how the development and function of T cells may be regulated by signals mediated through the TCR/CD3 complexes that contain normal and altered components.
   Role: P.I.

2. R21 AI44429 9/30/98 - 9/29/01
   National Institute of Health
   "Regulatory Mechanisms in Type 1 Diabetes"
   The major goal of the proposed study was to generate class II MHC tetramers to isolate disease-associated T cells and determine their roles in regulating the development of autoimmune diseases.
   Role: P.I.

3. R21 DK60190 9/30/01 - 9/29/03
   National Institute of Health
   "Regulation of Type 1 Diabetes Using Ribozymes"
   The major goal of the proposed studies is to design ribozyme based gene therapy approach to modulate the function of autoreactive T cells.
   Role: P.I.